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10/549,302	09/15/2005	Michael Hagen	AM100485	5958

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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/549,302	HAGEN, MICHAEL	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-56 and 59-101* is/are pending in the application.

4a) Of the above claim(s) *12-51 and 63-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-11,52-56 and 59-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 12-51 and 63-101 are withdrawn. Claims 6-7 and 57-58 are cancelled. Claims 1-5, 8-11, 52-56 and 59-62 are under consideration in this office action.

Withdrawal of Rejections

2. The following rejections have been withdrawn in view of applicants' amendments:

a) The new matter rejection of claim 8 under 35 U.S.C. 112, first paragraph;

b) The written description rejection of claim 8 under 35 U.S.C. 112, first paragraph;

Response to Arguments

3. Applicant's arguments filed September 8, 2009 have been fully considered but they are not persuasive.

Double Patenting

4. The double patenting rejection of claims 1, 8, 9, 52, 56, 59, 60 and 62 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 10, 13, 14,15, 24 and 25 of U.S. Patent No. 7,384,640 in view of Agren et al., (J. of Immunol. 1999. 162(2): 2432-2440) is maintained for reasons already of record.

The examiner acknowledges applicants request that the rejection be held in abeyance until patentable subject matter is determined. However the rejection will be maintained until the double patenting issue is resolved.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 52-56 and 59-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Neither the specification nor originally presented claims provides support for a method of immunizing a mammalian host against disorders associated with β-amyloid proteins comprising administering to the host an immunogenic amount of a composition comprising a cholera holotoxin (CT) and an Aβ 1-7 peptide antigen covalently associated with the CT, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid residue 29 of SEQ ID NO:2, wherein the mutation is not an aspartic acid, wherein the CT increases immunogenicity of the antigen.

Applicant alleges that support is found at page 76, lines 21-27 and page 12, lines 25 to 30. However at page 7, lines 21-27, the specification recites other embodiments

directed to methods of immunizing wherein the CT mutation increases immunogenicity of the antigen. Page 12, lines 25-30 is drawn to a number of antigens being conjugates to mutant CT E29H and conjugates being excellent immunogens in the absence of exogenous adjuvant. However there is no discussion of method of immunizing a mammalian host against disorders associated with β-amyloid proteins. Thus, there appears to be no teaching of the method as recited by claim 52

There is no disclosure of immunizing a host against disorder associated with b-amyloid proteins; there is no teaching as to what disorders are associated with β-amyloid proteins and which of those disorders can be immunized against with the immunogenic composition. At best the Examples teach that mice were administered with the immunogenic composition and the mice's antibody titer was increased and here is no disclosure of immunizing a host against disorder associated with β-amyloid proteins. Therefore, it appears that there is no support in the specification. Applicants must specifically point to page and line number support for the identity for a method of immunizing a mammalian host against disorders associated with β-amyloid proteins comprising administering to the host an immunogenic amount of a composition comprising a cholera holotoxin (CT) and an A 1-7 peptide antigen covalently associated with the CT, immunogenic composition comprising a cholera holotoxin (CT) and an Aβ 1-7 peptide antigen covalently associated with the CT additionally comprising the composition having one or more additionally noncovalently associated Aβ 1-7 peptide antigens. Therefore, the claims incorporate new matter and remain rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 52-56 and 59-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties,

functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.,* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative

number species to adequately describe a broad generic. *In Gostelli*, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus*. In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

The claims are drawn to method of immunizing a mammalian host against disorders associated with β-amyloid proteins comprising administering to the host an immunogenic amount of a composition comprising a cholera holotoxin (CT) and an Aβ 1-7 peptide antigen covalently associated with the CT, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid residue 29 of SEQ ID NO:2, wherein the mutation is not an aspartic acid, wherein the CT increases immunogenicity of the antigen and including a composition having one or more additionally noncovalently associated Aβ 1-7 peptide antigens.

The specification broadly describes immunogenicity studies. See the instant specification beginning at page 35. Thus the written description in this case fails to set forth a method of immunizing a mammalian host against disorders associated with β-amyloid proteins comprising administering to the host an immunogenic amount of a composition comprising a cholera holotoxin (CT) and an Aβ 1-7 peptide antigen covalently associated with the CT, having these abilities.

There was no immunogenicity test for the majority of the other mutants encompassed by claim 52 and there are no challenge experiments to determine whether a host was immunized against disorders associated with β-amyloid proteins. There is no disclosure of an immunogenic composition that immunizes against these

biological activities. There is no disclosure of any specific activity associated with β-amyloid proteins. There is no teaching of a method of immunization using the described holotoxin or a method with immunizes against unspecified disorders associated with β-amyloid proteins. With respect to claim 59, there is no disclosure of any compositions comprising one or more additional non-covalently associated Aβ 1-7 peptide antigens. Therefore the written description is not commensurate in scope with the claims. It is noted that applicants pointing the pages 7 and 12 of the instant specification does not address the lack of written description with regard to the instant claims.

In view of these considerations, a person skilled in the art would not have viewed the teachings of the specification sufficient to show that applicants were in possession of a method of immunizing a mammalian host against disorders associated with β-amyloid proteins comprising administering to the host an immunogenic amount of a composition comprising a cholera holotoxin (CT) and an Aβ 1-7 peptide antigen covalently associated with the CT, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid residue 29 of SEQ ID NO:2, wherein the mutation is not an aspartic acid, wherein the CT increases immunogenicity of the antigen and including a composition having one or more additionally noncovalently associated Aβ 1-7 peptide antigens as instantly claimed.

Applicants assertions are not found persuasive; thus the full breadth of the claims fails to meet the written description provision of 35 USC 112, first paragraph and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-5, 8-11, 52-56 and 59-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jobling et al., (WO/18434) in view of Agren et al., (J. of Immunol. 1999. 162(2):2434-2440) and Frenkel et al., (2000. PNAS. Vol.97(21):11455-11459).

Jobling et al., teach a composition comprising a mutant form of the Cholera toxin (CT) holotoxin that has reduced toxicity compared to a wild-type CT in an antigenic composition in order to enhance in a vertebrate host to a selected antigen from a pathogenic bacteria, virus, fungus or parasite (page 3-4, lines 31-3). Jobling et al., teach a point mutation an amino acid 29 of the A subunit wherein the glutamic acid residue is replaced by an amino acid other than aspartic acid (page 4, lines 4-8). The amino acid residue 29 is histidine (page 4, line 9). Jobling et al., teach other mutations within the A subunit are known, including positions 7, 11, 110 and 112 (page 10, lines 15-23). Jobling et al., teach encoded polynucleotides comprising the nucleic acid sequence of SEQ DIN O:1 wherein the sequences has a genetic modification of at least codon 29 of SEQ ID NO:1. See Example 1 teaching the oligonucleotide derived mutants created in plasmids and the construction of the plasmid encoding CT- with a nonconservative amino acid substitution (glutamic acid to histidine) at position 29 in the A subunit (See Example 1, at page 44).

Jobling et al., teach composition further comprises a diluent or carrier (page 4, lines 16-17). Jobling et al, teach the compositions further comprises adjuvants such as STIMULON™ QS-21, MPL™ (3-O-deacylated monophosphoryl lipid A), aluminum phosphate, aluminum hydroxide, IL-12, (page 39-40, lines 28-2). The vaccine antigens are from a wide variety of pathogenic microorganisms where the antigen comprises a one or more saccharides, proteins, protein subunits, or fragments, poly- or oligonucleotides, or other macromolecular components (page 40, lines 3-13). Jobling et al., teach that the compositions may contain more than one antigen from the same or different pathogenic microorganisms (pages 40-41). Jobling et al., teach the antigen and the mutant CT are administered at the same time (page 39, lines 15-17). However Jobling et al., do not teach that the cholera holotoxin and the Aβ 1-7 peptide antigen being covalently associated.

Agren et al., teach the adjuvanticity of the Cholera Toxin A1-based gene fusion protein; wherein the cholera and the antigen are covalently associated. Agren et al., teach the A1 subunit with a single amino acid change having comparable adjuvant function with that of the wild-type holotoxin (page 2432, col.1). Agren et al., teach a major breakthrough in immunomodulation and vaccine adjuvant design where they constructed a gene fusion that combined the enzymatic activity of the A1 subunit of CT with a B cell targeting moiety from an IgG-binding fragment of *Staphylococcus aureus* protein (page 2432, col. 2). The immunomodulator fusion protein composition was found to be completely nontoxic *in vitro* and *in vivo*. Agren et al., the administering the composition to mice (page 2433, col. 2). Agren et al., teach a promising now strategy for

vaccine adjuvant design and proves the concept that novel immunomodulators can be constructed as gene fusion proteins that target powerful bacterial enzymes, thereby avoiding harmful side effects (page 2432, col. 2). Agren et al., teach the construction of several mutants wherein the site mutations are at positions 7, 109 and 112 (page 2433, col.1). Thus, Agren et al., teach the ADP-ribosyltranferase activity as well as the Ig-binding ability which are critically required for the adjuvant function of the CT-A fusion protein (page 2433, col. 1).

Frenkel et al., teach immunization with Aβ 1-7 peptide antigen. Table 1 shows animals immunized with the Aβ 1-7 peptide antigen. Frenkel et al., teach epitopes within proteins comprising the EFRH peptide as fusion to its major coat protein were chosen and produced in large quantities (page 11455). Frenkel et al., teach immunization protocols also (page 11455-56).

Therefore it would have been prima facie obvious at the time of applicants' invention to apply Agren et al's covalently associated mutant cholera holotoxin and Frenkel et al., Aβ 1-7 peptide antigen to Jobling et al, immunogenic composition comprising a cholera holotoxin (CT) and an antigen, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid 29 of SEQ ID NO:2, wherein the mutation is not an aspartic acid, wherein the CT increases immunogenicity of the antigen, and method of immunization in order to provide novel immunomodulators constructed as gene fusion proteins that target powerful bacterial enzymes and enhance immune responses. One of ordinary skill in the art would have a reasonable expectation of success by incorporating covalently associated mutated CT and an

antigen, because no more than routine skill would have been required to covalently associated the CT and the antigen when the art already teaches co-administration; the avoidance of harmful side effects; and the diverse application for vaccine development when the same single amino acid mutation is well known in the art. Furthermore, no more than routine skill would have been required to incorporate the covalently associated cholera holotoxin and Aβ 1-7 peptide antigen of Agren et al., of Frenkel et al., for the available and functionally equivalent immunogenic composition of Jobling et al., comprising a cholera holotoxin and antigen, wherein the CT-A has a mutation of at least amino acid 29 of SEQ ID NO:2, since Agren et al., teach the criticality of both ADP-ribosyltranferase activity and Ig-binding ability for the adjuvant function of the covalently associated CT-A to advantageously achieve increased immunogenicity while maintaining it reduced toxicity characteristic.

Response to Arguments

8. Applicant's arguments filed March 30, 2010 have been fully considered but they are not persuasive.

Applicants assert that Jobling does not suggest covalently binding the mutant holotoxin to an antigen. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking the Jobling reference individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this case, Agren et al., teach the adjuvanticity of the Cholera Toxin A1-based gene fusion protein; wherein the cholera and the antigen are covalently associated. Agren et al., teach a major breakthrough in immunomodulation and vaccine adjuvant design where they constructed a gene fusion that combined the enzymatic activity of the A1 subunit of CT with a B cell targeting moiety from an IgG-binding fragment of *Staphylococcus aureus* protein. The immunomodulator fusion protein composition was completely nontoxic. Agren et al., teach vaccine adjuvant design and proves the concept that novel immunomodulators can be constructed as gene fusion proteins that target powerful bacterial enzymes, thereby avoiding harmful side effects. Agren et al., teach the ADP-ribosyltranferase activity as well as the Ig-binding ability which are critically required for the adjuvant function of the CT-A fusion protein. Therefore it is the position of the Office that Agren et al., clearly provides combining prior art elements such as the cholera toxins and antigens to known to yield predictable and beneficial results as based not on merely conclusory results but based on actual evidence wherein the combinations having enzymatic activity, such as the ADP-ribosyltranferase activity as well as the Ig-binding ability which are critically required for the adjuvant function of the CT-A fusion protein along with targeting abilities. The immunomodulator fusion protein composition was found to be completely nontoxic and avoids harmful side effects. The teachings, suggestions or motivations are provided by the prior art along with a teaching that one of ordinary skill in the art would have recognized that the results of the combination were predictable.

Applicants argue that neither Jobling, Argen or Frenkel teach or suggest conjugation of a mutant holotoxin to an Aβ 1-7 peptide for use in an immunogenic composition. However, Jobling et al., teach a composition comprising a mutant form of the Cholera toxin (CT) holotoxin and antigen within an antigenic composition. Argen teach the benefits of covalently associating the cholera toxin and antigen in order to retain the adjuvant function, avoid harmful side effects and combine enzymatic and targeting abilities. Finally, Frenkel et al., teach incorporating the Aβ 1-7 peptide antigen. There would have been a reasonable expectation of success in immunizing a host given Frenkel et al., demonstration of high titer antibodies with high binding specificity in a short period of time without the need for adjuvants and the self-expression of the Aβ 1-7 peptide antigen leading to long-last immunization. Therefore applicants arguments are not found persuasive and the rejection is maintained.

Conclusion

9. No claims allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/
Primary Examiner, Art Unit 1645